



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-D-0108]

Draft Guidance for Industry on Limiting the Use of Certain Phthalates as Excipients in Center for Drug Evaluation and Research-Regulated Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled “Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products.” This draft guidance provides the pharmaceutical industry with the Center for Drug Evaluation and Research’s (CDER’s) current thinking on the potential human health risks associated with exposure to dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP). In particular, the draft guidance recommends that the pharmaceutical industry avoid the use of these two specific phthalates as excipients in CDER-regulated drug and biologic products, including prescription and nonprescription products.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration,

10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>.

Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

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10903 New Hampshire Ave.,
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SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products.” This draft guidance provides the pharmaceutical industry with CDER’s current thinking on the potential human health risks associated with exposure to DBP and DEHP. In particular, the draft guidance recommends that the pharmaceutical industry avoid the use of these two specific phthalates as excipients in CDER-regulated drug and biologic products, including prescription and

nonprescription products. The recommendations in this guidance do not address the use of DBP or DEHP in other types of FDA-regulated products or exposure to DBP or DEHP due to the presence of any of these compounds as an impurity--including as a result of leaching from packaging materials.

Phthalate esters (phthalates) are synthetic chemicals with a broad spectrum of uses. Phthalates are found in certain pharmaceutical formulations, primarily as a plasticizer in enteric-coatings of solid oral drug products to maintain flexibility, but they also may be used for different functions in other dosage forms. Phthalates also are found in other products for uses such as softeners of plastics, solvents in perfumes, and additives to nail polish, as well as in lubricants and insect repellents.

Phthalates have been studied extensively in animals, and DBP and DEHP have been shown to be developmental and reproductive toxicants in laboratory animals. While the data in humans are less clear, epidemiological studies suggest that certain phthalates may affect reproductive and developmental outcomes. Other studies have confirmed the presence of DBP and DEHP in amniotic fluid, breast milk, urine, and serum.

Data from the National Health and Nutrition Examination Survey (NHANES) indicate widespread exposure of the general population to phthalates. Humans are exposed to phthalates by multiple routes, including inhalation, ingestion, and to a lesser degree absorption through the skin. Several observational human studies have reported an association between exposure to certain phthalates and adverse developmental and reproductive effects. The ubiquitous presence of phthalates in the environment and the potential consequences of human exposure to phthalates have raised concerns, particularly in vulnerable populations such as pregnant women and infants.

Although the currently available human data are limited, the Agency has determined that

there is evidence that exposure to DBP and DEHP from pharmaceuticals presents a potential risk of developmental and reproductive toxicity. While it is recognized that drug products may carry inherent risks, DBP and DEHP are used as excipients, and safer alternatives are available. Therefore, the Agency recommends avoiding the use of DBP and DEHP as excipients in CDER-regulated drug and biologic products.

These recommendations apply to CDER-regulated drug and biologic products that are under development (i.e., investigational new drugs), nonapplication products (e.g., over the counter monograph products), and both marketed approved products and those currently under review for marketing consideration (i.e., new drug applications, abbreviated new drug applications, and biologics license applications).

There are alternatives to DBP and DEHP for use as excipients in CDER-regulated products. Manufacturers with products that contain DBP or DEHP should consider alternative excipients and determine if the alternative excipient they plan to use has been used in similar CDER-approved products and at what level.

The Inactive Ingredients Database provides information on excipients present in FDA-approved drug products, and this information can be helpful in developing drug products. As manufacturers reformulate their products, the listings for DBP and DEHP will be removed from the Inactive Ingredients Database.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on limiting the use of certain phthalates as excipients in CDER-regulated products. It does not create or confer any rights for or on any person and does not operate to

bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. The Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520) and have been approved under OMB Control Numbers 0910-0014 and 0910-0001.

IV. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: February 28, 2012.

Leslie Kux,

Acting Assistant Commissioner for Policy.